Histopathological aspects of cutaneous lymphoma

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Cutaneous lymphoproliferative disorders are such a complex group of diseases that their detailed morphological features are most profitably discussed amongst specialists. However, many of the basic concepts have broad diagnostic relevance, and this article is written with the generalist predominantly in mind.

As in many branches of medicine, the key to the correct diagnosis in cutaneous lymphoproliferative diseases lies in interspecialty communication and clinicopathological correlation. In addition, because of the inherent difficulties and pitfalls in the diagnosis and management of cutaneous lymphoma, all cases should be discussed by a multidisciplinary team. Cutaneous lymphoma is so rare that some form of centralization of expertise would appear essential. Indeed, this constitutes a strong argument for the histology of all cases of cutaneous lymphoma to be reviewed by a specialist in a Calman cancer centre and where necessary the patients to be referred and discussed by the appropriate multidisciplinary team. An exciting development has been the foundation of the multidisciplinary United Kingdom Skin Lymphoma Group. The plan is for this to link directly into the well established European Organization for the Treatment of Cancer (EORTC) Cutaneous Lymphoma Group. Also, it is hoped that the multidisciplinary teams of cancer centres will link into the UK Skin Lymphoma Group, possibly through new or existing regional or subregional lymphoma groups. An important function of the UK Group will be to develop consensus guidelines and standards and to facilitate entry into national and international clinical trials; within the UK to date, there have been very few clinical trials with respect to cutaneous lymphoma.

WHAT IS THE DIAGNOSTIC GOLD STANDARD?

Contrary to widespread opinion, the gold standard for diagnosis of cutaneous lymphoma is not simply the histopathological appearance. Each case must be assessed in its own right and the diagnosis achieved by the amalgamation of several diagnostic indices. At a minimum, these must include clinical details, histopathology and the immunophenotype. Genotypic analysis is increasingly important and has become mandatory for accurate diagnosis of Sézary syndrome. Cytogenetic analysis, aetiology and the functional biology of the neoplastic cells can all have diagnostic relevance to particular subtypes of lymphoma. This approach is essential as none of these separately can claim 100% diagnostic sensitivity and specificity. This difficulty is compounded by the typically long evolution of cutaneous lymphoma before characteristic diagnostic features emerge. During this time of uncertainty, regular skin lymphoma meetings are essential, and should include haematologists, oncologists and perhaps at times clinical immunologists. In view of the long time-course in many cases, it is always prudent to review past biopsy material as well as current specimens at such meetings. Each of the main diagnostic pointers will be discussed briefly.

Clinical details

No histopathologist should ever diagnose cutaneous lymphoma without full knowledge of the clinical details. Failure to do so is a recipe for diagnostic disaster, and all too commonly the information on a clinical request form is insufficient. Ideally, this information should be obtained by personal examination of the patient as well as liaison with clinical colleagues.

The distinction between primary and secondary cutaneous lymphoma has major therapeutic and prognostic importance and accordingly all patients must be accurately staged. Until recently, designation of cutaneous lymphoma as primary required six months of follow-up from initial presentation without development of extracutaneous manifestations. This has now been replaced in most cases by intensive staging at the time of presentation. In particular, for cutaneous B-cell lymphoma (CBCL) this should include imaging and a bone marrow trephine biopsy.

Cutaneous lymphoma tends to present with a small number of clinical manifestations, but histological examination remains essential as each manifestation can be associated with different types of lymphoma. A fact to bear in mind is that these lesions sometimes regress spontaneously: clinicians tend to believe that lesions that show regression cannot be malignant. Also, many types of cutaneous lymphoma respond readily to treatment (especially radiotherapy) and in the early stages can show a long disease-free interval. Eventual relapse, however, is usual.

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Histopathology

When clinicians are taking a biopsy for histopathological examination, they must ensure that it is both a reasonable size and extends to the subcutaneous fat. Punch biopsies are wholly unsatisfactory.

An important skill of the histopathologist is disease recognition by pattern analysis. In cutaneous lymphoproliferative disorders, however, although the pattern analysis is helpful to a degree, no single pattern should be regarded as specific to one type of disease or cell lineage. Although one pattern is often associated with a short-list of candidate diseases or cell types, in reality any pattern can be associated with nearly any type of lymphoma. For example, epidermotropism is a frequent characteristic of T-cell infiltrates, but the phenomenon does not permit a reliable distinction between reactive and neoplastic disease processes. In addition, epidermotropism can be seen very occasionally in B-cell infiltrates and can even occur with non-lymphoid cells, as in Langerhans cell histiocytosis (histocytosis-X) or metastatic malignant melanoma. As a corollary, whereas a non-epidermotropic pattern is frequently seen in neoplastic B-cell infiltrates, the same pattern can also occur with neoplastic T-cell infiltrates. The intraepidermal cluster of lymphoctyes designated a Pautrier's abscess is often considered pathognomic of mycosis fungoides (MF). It can, however, be seen in any type of cutaneous T-cell lymphoma (CTCL) and can be closely mimicked by collections of epithelial cells, as in Merkel cell carcinoma.

Angiodestruction and tissue infarction are common features of lymphomatoid granulomatosis and natural killer cell lymphomas but angiocentricity can be seen in any cutaneous lymphoma. The same is true of other patterns such as infiltration into the subcutaneous fat (panniculitis-like cutaneous lymphoma) or blood vessels (intravascular lymphoma).

In short, histopathological examination usually generates a list of diagnostic probabilities and possibilities rather than absolute certainty. A fair assessment is that the pattern of disease, as seen by an experienced histopathologist, is of immense help in determining the presence or absence of cutaneous lymphoma. But the histopathologist must be ever aware of the limitations and exceptions.

Immunohistology

Immunophenotyping is important to the diagnosis of cutaneous lymphoproliferative disorders: in most instances it can identify the cell lineage of the neoplastic process. Fortunately, the most relevant antibodies all now work on paraffin sections, whereas in the past frozen sections were always required. The antibodies used should include those for T-cells (CD3, CD45 RO, helper/inducer CD4 and cytotoxic/suppressor CD8 subtypes), B-cells (CD20 and CD79a), their subtypes (CD5, CD10 and bcl-6), natural killer cells (CD56), histiocytes (CD68) and antigen presenting cells (S100 and factor 13A). In addition, all large cells should be immunophenotyped for the possible presence of CD30 and if positive the ALK-1 protein to investigate the possibility of t(2;5) translocation.

Interpretation of the findings can be difficult because of the basic cellular composition of any neoplasm. Every neoplastic lesion contains not only neoplastic cells but also reactive stromal cells. In some instances, the neoplastic cells will be present only in small numbers and can be easily mistaken for the reactive cell population. The classic example is the T-cell-rich variant of CBCL.

In common with the non-specificity of histological patterns, T-cell subtypes (such as CD2 cytotoxic/suppressor cells) can be associated with several different types of lymphoma and in addition each type has its prognostic implications. Likewise, no single disease is restricted to one cell subtype. MF, for example, although usually of CD4 helper/inducer type, can occasionally be of CD8 cytotoxic/suppressor type.

Genotypic analysis

The molecular demonstration of monoclonality in T-cells or B-cells, by the rearrangement of the T-cell receptor (TCR) or immunoglobulin heavy chain gene respectively, is a powerful diagnostic and prognostic tool. The technique, however, is not routinely available in all centres and the results, in the absence of good quality control, are subject to errors and misinterpretation.

Furthermore, the biological implications of the results are not absolute. Polyclonality and monoclonality do not always correlate with reactive and neoplastic disease. Both polyclonality and monoclonality can be associated with either benign or malignant biological behaviour. Also, rearrangements of the alpha–beta and gamma–delta chains of the TCR are not specific to any one type of CTCL and can vary within one disease between different cases. These subtypes can have different prognostic and therapeutic implications.

The development of the polymerase chain reaction (PCR) was a major scientific advance. However, although the more sophisticated variants of PCR have increased detection sensitivity, we have seen the advent of molecular diseases such as clonal dermatitis. We do not yet know how many of these evolve into lymphoma.

Whilst not all centres can offer this technique, PCR methodology is applicable to paraffin embedded material, so specimens are easily despatched elsewhere.

Other indices

Cutaneous lymphoma is sometimes associated with pathogens such as the human T-cell lymphoma/leukaemia virus, Epstein–Barr virus (EBV), human immunodeficiency virus, the human herpes virus type 8 or *Borrelia*.

In some cases, a useful subdivision can be achieved by the demonstration of granule-associated cytotoxic activity, by the identification of granzyme, perforin or TIA-1. In addition, there are intriguing data relating to the potential subdivision of CTCL according to the pattern of cytokine production. Sézary syndrome, for example, is usually derived from Th2 type cells. Possibly the biggest area of disappointment has the continuing failure to demonstrate a consistent cytogenetic abnormality that could have reliable diagnostic importance. For example, the exact incidence of trisomy 3 in primary marginal zone CBCL remains uncertain and it seems that t(14;18) translocation is absent in most cases of primary follicular centre CBCL. Furthermore, important genetic abnormalities such as *bcl-2* gene rearrangements do not correlate with bcl-2 protein expression. Indeed, paradoxically, cases of marginal-zone CBCL can be positive for bcl-2 protein despite the absence of t(14;18) translocation.

PSEUDOLYMPHOMA

Although the word pseudolymphoma has lost favour in histopathology circles, it is probably too entrenched in the parlance of clinical dermatology to be removed. Ideally, either the cause of the benign lymphoproliferation that is mimicking lymphoma should be stated (examples being drugs, insect bites, light sensitivity, tattoos and *Borrelia*) or, if it is not known, the condition should be classified as idiopathic cutaneous lymphoid hyperplasia. Of greatest importance is the appreciation that pseudolymphoma can closely mimic the architectural patterns of B-cell or T-cell lymphomas. Furthermore, many B-cell pseudolymphomas reported in the past were actually marginal-zone B-cell lymphoma. Jessner's lymphocytic infiltrate fits somewhere into this area but its exact nosological status remains uncertain. Many find it a useful holding diagnosis pending eventual evolution into a more specific benign or malignant disease process.

CLASSIFICATION OF PRIMARY CUTANEOUS LYMPHOMA

As aids to clinical management and prognostic evaluation, modern classifications tend to be based on clinicopathological entities. The EORTC classification was designed specifically with this objective in mind but, despite its undeniable popularity in mainland Europe, it has been criticized within the UK[1,2]. Proposals to apply the Revised European–American Classification of Lymphoid Neoplasms to the skin have been overtaken by a new general classification from the World Health Organization (WHO)[3]. The WHO proposals, however, are likewise imperfect and consensus on classification remains to be achieved[4]. Skin lymphoma is usefully divided into T-cell, B-cell and natural-killer-cell types. Cutaneous proliferations arising from histiocytes and antigen presenting cells (such as Langerhans cells) will not be discussed here. Similarly, primary cutaneous Hodgkin's disease is omitted in view of the debate as to whether it is a true primary cutaneous entity.

PRIMARY CUTANEOUS T-CELL LYMPHOMA

Mycosis fungoides

MF arises from a cerebriform T-lymphocyte and by definition must conform to the Alibert–Bazin clinical spectrum of disease, with potential progression through patch, plaque and tumour stages. On this basis, histopathologists cannot definitively diagnose CTCL as MF until they are aware of the clinical picture.

With the advent of more specific histopathological criteria and the availability of genotypic analysis, the requirement to diagnose premycotic eruptions has diminished substantially. Similarly, entities such as large-plaque parapsoriasis are now increasingly believed to represent MF[5].

In general, MF remains indolent for many years, although eventually it may transform to large-cell lymphoma. The most appropriate clinical management of MF relates principally to the stage of the disease.

Sézary syndrome

Generalized erythroderma by definition involves over 80% of the skin surface. This is not restricted to Sézary syndrome and can occur both in benign dermatoses and in almost any type of CTCL. Although there is surprisingly no universally agreed definition of Sézary syndrome, most authorities would now accept the requirement to demonstrate a clonal T-cell population, an absolute Sézary cell count within the peripheral blood of over 1000/μL or Sézary cells representing 10% of the leucocyte population and an expanded CD4 T-cell population as reflected by a CD4:CD8 ratio of greater than 10. Despite the aggressive biological nature of Sézary syndrome, the histopathological appearance can be non-diagnostic.

Cutaneous CD30 T-cell lymphoproliferative disorders

These represent a fascinating spectrum of disease, extending from lymphomatoid papulosis (LYP) through to CD30 large-cell lymphoma. The latter can display anaplastic, pleomorphic or immunoblastic features. However, it is the

clinical rather than the histopathological features that are decisive in diagnosis. The presence of a chronic recurrent self-healing papular–nodular skin eruption favours LYP whereas a solitary persistent lesion favours lymphoma. Cases that are clinically lymphoma are still regarded as lymphoma even if the histology shows the polymorphic features of LYP. Similarly, clinical cases of LYP are regarded as borderline LYP even if the histology shows monomorphic features usually more characteristic of lymphoma. The difference between LYP and lymphoma is clinically vital since LYP represents a largely indolent (though incurable) disease that does not warrant aggressive treatment.

The CD30 antigen is not lineage specific and was first described in relation to the Reed–Sternberg cell of Hodgkin's disease. The importance of CD30 in the skin is to identify this group of disorders: moreover, large-cell lymphomas that are CD30 positive generally have a better prognosis than those that are negative. CD30 large-cell lymphoma can also result from transformation of MF, but this is generally considered outwith the consideration of primary CD30 disease.

There is an interesting relationship between LYP, CD30 anaplastic large cell lymphoma, MF and Hodgkin's disease. Perhaps the most revealing observation has been that these apparently disparate diseases, on a clinical and histopathological basis, can be associated with the same T-cell receptor gene rearrangement when the diseases occur in the same patient over the course of time. Unlike its nodal counterpart, CD30 anaplastic large-cell lymphoma of the skin is not usually associated with a t(2;5) translocation.

Other types of CTCL

Three types of CTCL can have special relevance to the generalist. First, subcutaneous panniculitis-like CTCL can be associated with the haemophagocytic syndrome. Second, angioimmunoblastic T-cell lymphoma can be associated with numerous peripheral blood abnormalities including raised immunoglobulin levels. Third, so-called cytoxic lymphomas illustrate the phenotypic diversity that can be associated with one biological function. These lymphomas can be CD4, CD8 or CD56 phenotype and may have a poor prognosis.

PRIMARY CUTANEOUS B-CELL LYMPHOMA

Marginal-zone and follicular-centre CBCL

For nearly a decade there has been debate about whether one or both of these types of CBCL exist. To a degree, however, this debate has lacked clinical relevance since this group is generally associated with a good long-term prognosis. Most authorities now agree that both types exist and the debate now centres on their comparative incidence and the best diagnostic criteria. In brief, the currently unpublished experience of the UK Skin Lymphoma Group is that follicular-centre lymphoma tends to be CD10 positive, whereas marginal-cell lymphoma is CD10 negative. Marginal-zone lymphoma belongs to the mucosa-associated lymphoid tissue (MALT) type of lymphoma and, like *Helicobacter pylori* with gastric lymphoma, *Borrelia burgdorferi* has been associated with CBCL. Whether antibiotic therapy is as useful in CBCL as it is in MALT lymphoma remains to be seen.

Diffuse large-B-cell lymphoma (DLBCL)

Most cases of DLBCL have a similar prognosis to marginal-zone and follicular-centre lymphoma and in some instances there is histological evidence that DLBCL has arisen from one of these two types of lymphoma. The EORTC proposes that DLBCL on the legs of elderly patients has a less favourable prognosis, but this is not universally agreed.

Intravascular large-B-cell lymphoma

Although rare, this lymphoma is important in general medicine in view of its tendency to present with both skin and central nervous system manifestations and in view of its very poor prognosis. Some of the manifestations relate directly to the occlusion of blood vessels by malignant cells and ischaemic sequelae.

CUTANEOUS NATURAL-KILLER/NATURAL-KILLER-LIKE T-CELL LYMPHOMA

This cutaneous lymphoma has only recently been defined and is principally characterized by CD56 positivity and cytotoxic activity[6]. Histologically, the lymphoma often shows angiocentricity and, clinically, most cases respond poorly to treatment and have a poor prognosis. Because of similarities with nasal natural-killer-cell lymphoma (which is commonly Epstein–Barr virus positive), those in the skin are often referred to as nasal-type.

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